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Research Article

A clinical trial of treatment of uncomplicated typhoid fever: efficacy of ceftriaxone-azithromycin combination

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ABSTRACT

Background: Typhoid fever is a systemic infection caused by Gram-negative bacterium *Salmonella enterica serovar typhi* (*S. typhi*). It is a major health problem in India. It carries significant morbidity and mortality. Antimicrobial therapy is critical for the management of typhoid fever. Emergence of multidrug-resistant (MDR) and nalidixic acid-resistant (NAR) strains of *S. typhi* has complicated therapy by limiting treatment options. Hence, this study was conducted to evaluate the efficacy and safety profile of ceftriaxone and azithromycin combination therapy in uncomplicated typhoid fever.

Methods: Adults patients of blood culture proven uncomplicated typhoid fever admitted in the medicine ward of Teerthanker Mahaveer Medical College and Research Centre were treated with ceftriaxone intravenously (2 g daily for 14 days) and azithromycin orally (500 mg daily for 7 days). Patients were clinically and bacteriologically evaluated during the study period and follow-up.

Results: 96% cure rate was observed. No relapse was recorded.

Conclusion: Ceftriaxone-azithromycin combination may be considered as an empirical therapy for treatment of uncomplicated typhoid fever in view of the emergence of MDR and NAR strains of *S. typhi*.

Keywords: Typhoid fever, Ceftriaxone, Azithromycin

INTRODUCTION

Typhoid fever is an acute, generalized infection of the reticuloendothelial system caused by *Salmonella enterica serovar typhi* (*S. typhi*). It is most often acquired through consumption of water or food that has been contaminated by feces of acutely infected or convalescent person or a chronic asymptomatic carrier. The onset of illness is gradual. Fever increases daily from low-grade to as high as 102-104°F (38-40°C) by the 3rd-4th day of illness. It is associated with headache, malaise, and loss of appetite. There may be hepatosplenomegaly and a macular rash on the trunk. Life-threatening complications can occur after 2-3 weeks of illness. Diagnosis is made by blood, bone marrow, or stool culture. Specific antimicrobial therapy shortens the clinical course of typhoid fever and reduces the risk of death.[1]

For decades, chloramphenicol has been highly effective against *S. typhi,* but multi-drug resistant (MDR) strains of *S. typhi* (resistant to chloramphenicol, trimethoprim-sulfamethoxazole, and ampicillin) has restricted its use in typhoid fever. Fluoroquinolones have proven to be effective for MDR cases of typhoid fever.

However, nalidixic acid-resistant (NAR) isolates of *S. typhi* have reduced susceptibility to fluoroquinolones, and hence typhoid fever caused by these isolates responds less well to fluoroquinolone therapy. Resistance to NA has been rising in India since 2005 and is currently 100%.[2,3]

Ceftriaxone is highly effective in typhoid fever, but it is less than ideal alternative drug for the treatment of uncomplicated typhoid fever. It shows a slow response with mean time of 5-7 days or even longer to defervescence, which could be attributed to poor penetration capability of the drug into the cells, and thus difficult to eradicate the bacteria from the intracellular niche. Extended spectrum beta-lactamase (CTX-M-15 and SHV-12 ESBLs) and CMY-2-AmpC beta-lactamase producing *S. typhi* has been reported. Rise in resistance to third or fourth generation cephalosporins has been observed in many studies.[4] Azithromycin possesses many characteristics for effective and convenient treatment of typhoid fever, and hence, it is a further option. Azithromycin resistant strains of *S. typhi* has recently been reported in India.[5,6]

Over last few years, preliminary published data have proven combination therapy of intravenous ceftriaxone with oral azithromycin significantly superior to ceftriaxone alone albeit in a small group of non-immunized travellers who acquired typhoid fever in the Indian subcontinent.

The current study goal is to examine the efficacy of ceftriaxone and azithromycin combination therapy for the treatment of uncomplicated typhoid fever.

METHODS

The present prospective study was conducted in Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, India, during the period from March 2014 to January 2015. The study was approved by Institutional Ethic Committee.

Totally, 25 patients of typhoid fever admitted in the medicine wards were selected for the study. In all cases, blood culture was positive for *S. typhi*. Antimicrobial susceptibility test (AST) of isolates to chloramphenicol, trimethoprim-sulfamethoxazole, ampicillin, ciprofloxacin, ofloxacin, ceftriaxone, and azithromycin was also performed. Blood culture from patients was processed by BACTEC 9240 blood culture automated system (Becton Dickinson). ID (identification) and AST were determined by BD Phoenix 100 automated microbiology system.

Routine investigations e.g., electrocardiogram, echocardiography, and radiography (X-ray chest, sonography chest, and abdomen), complete blood count, bone marrow examination, serological test for malaria, urinalysis, liver function tests, and renal function tests were done in each patient.

Inclusion criteria

(a) Adult, (b) uncomplicated typhoid fever, (c) blood culture positive for *S. typhi*, (d) isolates susceptible *in vitro* to ceftriaxone and azithromycin, (e) signed informed consent to participate in the study, (f) patient able to take oral medications.

Exclusion criteria

(a) Allergy to cephalosporins or macrolides, (b) typhoid fever associated with complications e.g., intestinal perforation, intestinal bleeding, shock, and encephalopathy, (c) inability to swallow oral medication, (d) underlying illness, (e) pregnancy, (f) lactation, (g) treatment within the past 4 days with an antibiotic that may be effective against typhoid fever.

A specially designed proforma was prepared and data pertaining to the patients were recorded in it. Data included demographic details, symptoms and signs, clinical course including temperature measurement, and outcome including complications, relapse and bacteremia and disposition (discharged, transferred, died).

All study group patients were treated with a combination of intravenous ceftriaxone 2 g daily for 14 days with oral azithromycin 500 mg daily for the first 7 days.

Supportive treatment included paracetamol tablet and intravenous dextrose infusion when indicated. The patients

were given semisolid diet to liquid balanced diet throughout the therapy.

Each day, every case was clinically evaluated twice daily (morning and evening) in the ward and oral temperature recorded. Blood culture was repeated at the end of treatment (day 14). Each patient remained hospitalized throughout the treatment period and next 3 days after therapy was completed. Patients were followed up once weekly for 1-month after end of the therapy for relapse of symptoms. Stool cultures were performed after the treatment and repeated at 1, 3 and 6 months later for *S. typhi*.

Primary outcomes of interest were: (a) Treatment failure, defined as persistence of fever after 7 days of treatment or development of complications under the treatment, (b) microbiological failure, defined as a positive culture from blood at the end of treatment, (c) relapse, defined as recurrence of symptoms in addition to a positive culture from blood or stool within 1-month during follow-up period, (d) adverse drug reaction, defined as an injury related to medical management, in contrast to complications of disease, (e) fecal carrier.

Secondary outcomes included

(a) Fever clearance time (FCT), defined as time in hours from the start of the trial drug until body temperature falls to values <37.50°C and remains so for 48 hrs. (b) Duration of hospital stay, defined as time in days from entry into trial until discharge.

Patients were considered clinically cured when fever subsided within 7 days of antibiotic therapy and without any relapse during 1-month follow-up period.

Statistical analysis of data

All the data were calculated by SPSS software version 15.0. The parametric variables were defined as mean ± standard deviation.

RESULTS

Totally, 17 out of the 25 patients were males (68%) with a male to female ratio of 2.1:1. Age of all patients ranged between 18 and 47 years. Mean age of patients was 27.38 years (Table 1).

Mean duration of fever in the study group was 9.20 days (Table 2). Mean time to become afebrile was 4.88 days. FCT was <5 days in 23 (92%) and in 1 (4%) case fever settled in 7 days. Treatment failure was observed in 1 (4%) case. There was no relapse in cured cases (Tables 3-5).

Two patients (8%) experienced minor adverse effects: nausea and pain abdomen and were managed easily. No carrier state was noted. Stool culture remained negative during follow-up 6 months period in all treated cases. Cost of ceftriaxone and azithromycin treatment in one patient was 1830 INR.

Table 1: Age and sex distribution in the typhoid fever patients.

Age group	n (%)		
	Male	Female	Total
18-22	5 (20)	2 (8)	7 (28)
23-27	6 (24)	2 (8)	8 (32)
28-32	4 (16)	-	4 (16)
33-37	1 (4)	2 (8)	3 (12)
38-42	-	-	-
43-47	1 (4)	2 (8)	3 (12)
Total	17 (68)	8 (32)	25 (100)

Mean age: 27.38±9.13 years

Table 2: Duration of fever in the typhoid fever patients before starting treatment.

Duration of fever	Patients n (%)
≤7 days	7 (28)
8-14 days	16 (64)
>14 days	2 (8)

Mean duration of fever: 9.20±3.86

DISCUSSION

Meltzer et al. conducted a comparative trial of ceftriaxone - azithromycin combination therapy versus ceftriaxone monotherapy on 37 patients suffering from enteric fever (*Salmonella* paratyphi A infection) and reported that combination therapy may provide therapeutic advantage over monotherapy. Time to defervescence in 17 patients treated with ceftriaxone and azithromycin combination was 3.2 days, whereas in 13 cases treated with ceftriaxone monotherapy, the time to defervescence was 6.6 days.

The present study conducted a trial of ceftriaxone and azithromycin combination on 25 patients suffering from typhoid fever caused by *S. typhi* observed defervescence in 4.88 days.

Treatment of typhoid fever has been complicated in recent years by the rise of MDR strains including quinolone/NAR *S. typhi* (NARST). The preferred regimen for NARST is a 10-14 days course of ceftriaxone.[7]

Antibiogram of *S. typhi* isolates from blood in coastal Karnataka region of India revealed these strains to be highly susceptible to ceftriaxone.[8]

Table 3: Response to therapy in the typhoid fever patients.

Total (n)	Good response* (n)	Moderate response** (n)	Poor response*** (n)	No response (n)
25	1	22	1	1

*Temperature settling in 3 days, **Temperature settling in 3-5 days, ***Temperature settling in >5 days

Table 4: Reduction of body surface temperature (°F) in the typhoid fever patients.

Days	Temperature (°F)	
	Mean	SD
Day 1	102.34	0.9
Day 3	99.90	0.7
Day 5	98.42	0.3
Day 7	98.20	0.2

SD: Standard deviation

Table 5: FCT in the typhoid fever patients.

Group	Mean±SD
Typhoid fever patients	4.88±0.53 days

FCT: Fever clearance time, SD: Standard deviation

However, response to ceftriaxone is slow. Median time to defervescence in more than 10 days has been reported in some studies. The delayed response to it may reflect the intracellular location of *S. typhi*, where ceftriaxone is less active.[9]

Jain and Das Chugh has recently reported resistance to ceftriaxone in 1% strains of *S. typhi*, at Delhi, India. Garg et al. noted 2.5% strains of *S. typhi* resistant to ceftriaxone at Shimla, Himachal Pradesh, India.

Azithromycin has been reported to be as effective as ceftriaxone in the treatment of typhoid fever. The efficacy of azithromycin during treatment is related to tissue concentration rather than serum concentration.[10,11] Azithromycin is also rapidly cleared from circulation. Azithromycin resistance leading to treatment failure has been reported by Molloy et al.

Azithromycin resistance rate to *S. typhi* has increased from 2.6% to 17.6% in India. It is a matter of concern.[12]

Ceftriaxone exerts its maximum effect in the extracellular compartment. The azithromycin shows excellent penetration into most tissues, and it achieves concentration in macrophages and neutrophils that are more than 100-fold higher than the concentration in serum, so it exerts its maximum effect in the intracellular compartment. Their combination may confer additional benefit. Hence, a novel approach was proposed to combine both the drugs for treatment of typhoid fever.[13-16]

The combination of these two drugs (ceftriaxone and azithromycin) has become standard practice in Israel. The combination needs further trials for evaluation of efficacy and safety profile in the Indian context, so that it might be recommended as empirical therapy for treatment of typhoid fever in endemic areas.

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